Biocomplexity Faculty Search Committee,
c/o Prof. Rob de Ruyter van Steveninck,
Biocomplexity Institute, Indiana University,
Swain Hall West 117, Bloomington, IN 47405-7105

25 Nov 2003

Dear Sir,

I am interested in a faculty opening in biocomplexity in your department.
I am a theoretical biophysicist and an expert in computer simulations. I have teaching and postdoctoral research experiences.

I enclosed my CV, publication list, research and teaching statements, as well as the names of five references who will provide recommendation letters on my behalf.

Sincerely yours,
Dr. D. Battogtokh,

Postdoctoral research associate,
Department of Biology,
Virginia Tech, 24061, VA

I. RESEARCH STATEMENT OF DR. D. BATTOGTOKH

A. Overview

I am interested in dynamics, pattern formation and self-organization of complex systems, where complexities arise not only from nontrivial, individual dynamics of elementary units, but also from strong nonlinear interactions between different modules containing these units. A population of biological cells is an example of such a complex system. Here, an elementary unit may represent a protein inside a given cell, which is itself an element of a nonlinear dynamical system of a gene regulation network. Another level of complexity arises from cell to cell communications which can be the control mechanism for cells' individual dynamics. The study of such complex systems require exact mathematical formulation and analysis, development of efficient computer codes, large scale simulations including parallel computations, and visualization of simulation data.

Mathematical formulation. The complex systems can be described by a general mathematical model,

$$\dot{\mathbf{X}}_\mathbf{i} = \mathbf{F}(\mathbf{p}, \mathbf{X}, \nabla, \Delta) + \mathbf{g}(S(\mathbf{r}_i, t)) \tag{1}$$

$$\epsilon \dot{S} = -\gamma S + D\Delta S + \sum_{j=1}^{N} h(\mathbf{X_j})\delta(\mathbf{r} - \mathbf{r_j}). \tag{2}$$

In the above equations a vector $\mathbf{X}$ represents a dynamical variable, for example, it may represent concentrations of chemical compounds. $\mathbf{F}$ is a nonlinear function of $\mathbf{X}$, its gradients and diffusion. $\mathbf{p}$, D, γ, and $\epsilon \to 0$ are parameters. S is an inactive, fast, diffusive variable, whose role is coupling different $\mathbf{X}_i$'s by a function $\mathbf{g}$. Production of S depends on $\mathbf{X}$ through a function $h(\mathbf{X})$. In the case of a population of biological cells, $\mathbf{X_i}$ may represent protein levels in the cell with index i. Then, S can be a concentration of a signal molecule, produced inside the cells, through which the cells communicate.

I believe that Eqn. (1-2) will give a great impact in study of complex systems. Synchronization, collective motions, and irregular dynamics in different disciplines, from sociology to biology, can be described by the general mathematical model Eqn. (1-2).

I studied different versions of Eqn. (1-2) for different problems in physics, chemistry and biology. In the next three pages, I briefly outline my research with Eqn. (1-2).

B. Research on continuous time systems

1. Derivation of reduced universal forms

Generally speaking, no analytic techniques exist for treatment of Eqn. (1-2), when **F** is a nonlinear function. However, near the Hopf bifurcation, Eqn. (1-2) can be reduced to universal equations for amplitude and phase of oscillations, which can be analytically treated and are very convenient for numerical studies. I derived the universal equations from several biological models.

2. Simulation of Eqn.(1-2)

For years, using different numerical methods, I developed computer codes to study Eqn. (1-2). When I was a postdoc at Center for Simulation Physics, UGA, Athens, GA, I developed a parallel code for space dimension two. I also developed computer codes for visualization of simulation data.

3. Regulation of biochemical reaction networks

In well stirred systems, for example in a small volume of a cell compartment, diffusion and coupling by S field can be discarded. For such cases, Eqn. (1-2) can be reduced to a kinetic model, nonlinear ordinary differential equations (ODE). Many important problems such as enzymatic kinetics, gene regulation, and cell cycle can be studied by systems of ODE's.

Resonance in chains of enzyme-substrate reactions. In the group of Prof. E. E. Sel'kov(Pushino, Russia) , we studied complex enzyme-substrate reactions leading to oscillatory dynamics. We studied stability of oscillations against periodic perturbations of parameters and variables, and established resonance conditions [1].

Gene regulation in QA cluster of Neurospora crassa. In the group of Prof. J. Arnold(UGA, Athens, GA), we studied the quinic acid (QA) gene regulation network of *Neurospora crassa.* We developed a new method, a combination of Monte Carlo and kinetic simulations, called *Ensemble method*, for identification of parameters of large reaction networks [2]. We developed a mathematical model for the QA cluster and compared mRNA

levels measured in the experiment with our simulation data.

Cell cycle regulation In the group of Prof. J. Tyson(Virginia Tech,VA) , we studied bifurcation analysis of budding yeast cell cycle [3]. We also developed and analysed a generic model for cell cycles in different organisms: frog eggs, fission yeast and budding yeast.

4. Dissipative structures and turbulence in CO oxidation

When $\sqrt{D} >> (L, l_p)$, Eqn. (1-2) describe globally coupled systems. Here, L is a system size and l_p is a wavelength of characteristic patterns in the system. Surface catalytic reactions of CO oxidations is an example of globally coupled systems. In this case, $\mathbf{X}$ represents concentrations at elementary surface elements , while S field represents a fast mixing, global concentration in the air phase. In the group of Prof. A. S. Mikhailov(FHI, Berlin, Germany), we studied dissipative structures and turbulence in systems with global coupling. Several of our theoretical predictions were confirmed in experiments [4].

5. Front propagation and pattern formation in reaction diffusion systems

When $\sqrt{D} << (L, l_p)$, Eqn. (1-2) describe locally coupled, reaction diffusion systems. I studied front propagations in a reaction diffusion system exhibiting pattern formation. Also, I studied pattern formation of a front in an externally forced reaction diffusion system [5].

6. Multiaffine turbulence in a population of biological cells

When $l_p << \sqrt{D} << L$, Eqn. (1-2) describe nonlocally coupled systems. Research efforts on nonlocally coupled systems have started recently. In the group of Prof. Y. Kuramoto(Kyoto,Japan), we found that a population of hypothetical biological cells displays a similar type turbulence as fluids [6]. We derived a new self-consistent equation for nonlocally coupled phase model and found an analytic solution for it. I found Turing-Hopf mixed mode solutions in nonlocally coupled systems. I also derived conditions for a weak turbulence in the nonlocally coupled phase equation. My parallel simulations revealed that nonlocally coupled systems display chaotic fronts which, unlike fronts in locally coupled systems, can be stable to strong external perturbations.

C. Research on discrete time dynamics, stochastic simulations

For some complex systems, individual dynamics displayed by the units can be simple, for instance, the dynamics are switches between the discrete states, active(1) and inactive(0). Coupling between the units in these systems can be simplified by replacing a Laplacian operator by certain rules. Such a discrete modeling of complex systems is called cellular automata. With cellular automata modeling, I studied pattern recognition in the multilayer Hopfield neural networks. I also used cellular automata modeling for interactions between spiral waves and target patterns in excitable media.

In some complex systems, internal or external noise rules dynamics. For instance, in a small volume with a few interacting species, stochastic effects can not be discarded. I studied with molecular gas dynamic modeling CO oxidation [7], and gene expression [2]. I also simulated stochastic differential equations with multiplicative random process [3]. I developed a code for stochastic partial differential equations , .i.e., when Eqn. (1-2) include noise terms.

List of cited papers

1. E. E. Selkov, T. Chuluun and D. Battogtokh, "Multiresonance Phenomena in an Open Enzymic Reaction", Studia Biophysica, 1991, 31, 137.

2. D. Battogtokh, D. K. Asch , et. al.," An Ensemble Method for Identifying Regulatory Circuits with Special Reference to the QA Gene Cluster of Neurospora Crassa", PNAS USA, 99, 16904, 2002.

3. D. Battogtokh and J. Tyson, "Bifurcation Analysis of A Budding Yeast Cell Cycle Model", preprint.

4. D. Battogtokh, A. Mikhailov, "Controlling Turbulence in the Complex Ginzburg Landau Equation", Physica 90 D, 1996, 84

5. Y. Kuramoto, H. Nakao, D. Battogtokh, "Multiscaled Turbulence in Large Populations of Oscillators in Diffusive Medium", 288 Physica A, 244, 2000.

6. D. Battogtokh, "Front Instabilities in A Forced Oscillatory Medium with A Global Coupling", Phys. Rev. E., 66, 066202, 2002.

7. D. Battogtokh and B. Davaanyam, "Nonlinear Effects in Site Blocking Induced Oscillations", arXiv:condmat/0303019.

II. RESEARCH PLAN

A. A Short Term Research Plan

Realistic mathematical models play imporant roles in theoretical biology. One of the characteristic features displayed by these models is birhythmicity, oscillations with two different frequencies and amplitudes. Despite intensive studies of realistic models, we know only an informal condition for birhythmicity for two variable systems: double negative slopes obeyed by one of the nullclines. Therefore, it is desirable to formulate conditions leading to birhythmicity in terms of bifurcation theory, for multi-variable systems. Moreover, a theoretical study is needed to find conditions for switching of oscillations between different orbits by external forcing, by diffusion, and by internal fluctuations. I have some preliminary results on birhythmicity in the glycolytic model, a cell cycle model and the amplitude equation for byrithmic media.

If I will be selected for a faculty position, I would like to continue research on byrithmicity. One of my goals is to determine the role of birhythmicity in regulation of biological systems. My research plan on byrithmicity includes:

- finding quantative expressions for the saddle loop bifurcations driven by Michaelis(Goldbeter-Koshland) type functions, as they are the mechanism for birhythmicity
- simulation of birhythmic media in one and two space dimensions
- derivation of the Complex Ginzburg Landau(CGLE) and the phase equations from the glycolitic and cell cycle models
- derivation of the amplitude equation which exhibits saddle loop bifurcations
- characterization of birhythmic turbulence, computation of Lyaponov exponents, correlation functions
- simulation of autonomous target patterns in byrithmic media
- external forcing of birhythmic oscillators
- simulation of the effects of stochastic noise on birhythmic oscillators
- visualization of simulation data by computer movies

I will involve in this research graduate students. They will learn analytic techniques, computer simulations and visualizations. Our research results will be reported in scientific meetings and published in international journals.

B. A Long Term Research Goal

Cancer study is one of the challenging areas of theoretical and computational biology. I believe that mammalian cell cycle modeling will provide a crucial contribution in cancer research efforts. Recently, significant progress has been made in modeling of cell cycles in yeasts and frog eggs, but to my knowledge, a systematic research on mammalian cell cycle modeling has not yet been started. Obviously, mammalian cell cycle modeling is a very *serious* problem, it may take many years of hard work of many scientists. If I will be selected for a faculty position, I am committed to contribute to mammalian cell cycle modeling. I have some ideas how to conduct a systematic study on mamalian cell cycle. At this stage, however, I have formulated only the first steps of my research plan.

• *Mathematical model for mamalian cell cycle.* A wiring diagram for mammalian cell cycle is known, but it is very complex and updated constantly. Hopefully, my experience on mathematical modeling of cell cycles in frog eggs and yeasts will be very helpful in converting the mammalian cell cycle wiring diagram into a set of differential equations. Computer tools, such as *Gepasi* and *JigCell*, will be very helpful for such integrative modeling. However, an important difference will be made in the source codes for simulation, the code will be modular, i.e., the differential equations, modeling different modules of the wiring diagram, will appear in different subroutines. Such strategy will help in classification of modules according to their functions, time scales and roles in regulation. It will also save simulation time, as in mutants entire modules can be knocked out.

•*Parameter identification.* A mathematical model for mammalian cell cycle will have hundreds of parameters. It is expected that most of their actual values will be unknown. Therefore, the central problem is identification of these parameters. Hopefully, the ensemble method we developed for study of large reaction networks will be very helpful. However, the parameter ensemble obtained with the method will go through several filtering steps before being used for actual simulations of the model. First, the parameter ensemble will be sorted into sub-groups according to what bifurcations they generate. Then, the sub-groups that lead to dynamics in agreement with cell cycle physiology will be selected. They will go through an another filtering by comparing simulations with kinetics from experiments. The goal of the first phase of research will be accomplished , if the model and the selected parameters can successfully simulate main experiments on mammalian cell cycle.

III. TEACHING STATEMENT OF DR. D. BATTOGTOKH

My teaching experience include three courses, *Mathematical Biology*, *Theory of Solid State Physics* and *Nonlinear Dynamics*. The two semester course, Mathematical Biology, I taught at Mongolian State University, was mainly based on L. Edelstein-Keshet's book Mathematical Models in Biology. I also used J. Murray's book, Mathematical biology. The main topics of this course were basic models in ecology and population biology, phase plane and bifurcation analysis, epidemiology and infectious diseases, diffusion and advection. The two semester graduate course, Theory of Solid State Physics, I taught at Mongolian State University, was based on the classic books by Ziman, Principles of the Theory of Solids and by Abrikosov et. al., Methods of Quantum Field Theory in Statistical Physics. The main topics of this graduate course were electrons in crystals, Hartree-Fock approach, quasi-particles, electron phonon interactions, superconductivity. Finally, the two semester graduate course on Nonlinear Dynamics that I taught at Mongolian Pedagogical University, was based on two books, by E. Ott, Chaos in Dynamical Systems and Y. Kuramoto, Chemical Oscillations, Waves and Turbulence. The first part of this course discussed chaos in autonomous systems, the second part discussed spatio-temporal chaos.

For my eight years of postdoc at different Labs, I shared office with many students. I think that I helped many of them in making quick progress in their research. As a theoretical physicist, I always try to give to students a very clear and simple explanation of a problem. And as a interdisciplinary scientist, I try to look into the problems from unifying elements of science. It is essential to tell to students how problems arise from real world applications.

If I will be selected for a faculty position, I would like to develop an interdisciplinary course on scientific computation. I think that teaching analytic skills is very important even for a course on computation. I will pay special attention in derivation and analysis of mathematical models from basic principles, as the correct mathematical formulation of a problem is the starting point of any computations. Today many students can use softwares like *Mathematica*, *Matlab*, *Maple* etc., but learning numerical methods and algorithmic programming languages is also important. Students who can write computer codes design a better problem-solving strategy.

The interdisciplinary course on scientific computation will focus on four main topics:

- mathematical formulation of problems and rendering a mathematical model in a suitable

form for computation

- elementary(e.g. Runge-Kutta method) and high level simulation algorithms(e.g., Monte Carlo method, spectral methods)
- data mining and analysis (e.g., Salford)
- visualization of simulation data(IDL, PW-WAVE)

Students will learn this course by studying broad scientific problems, such as estimations of fish biomass in water resources, gene regulation, modeling gene expression data, fluid dynamics, spin waves, propagation of reaction fronts, pattern formation and chemical turbulence. One of the main goals of this course will be to make students comfortable and familiar with computation , so that they will be able to learn new methods and algorithms on their own.

My long term educational goal is to convert the course on scientific computation into Virtual labs, Web-based software applications designed to provide a flexible user-friendly environment for simulating complex systems. They will be written in the Java object-oriented programming language and are run on a "virtual machine" that can be implemented on any platform. As a result, virtual labs can be accessed not only in the classroom or campus computer labs, but from any machine connected to the Internet. This feature allows students greater freedom in working with virtual labs and makes these tools ideal for distance learning, education for the severely disabled, and other non-traditional modes of instruction.